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EXAMINER

[illegible]

[illegible]

ART UNIT	PAPER NUMBER
[illegible]	22

DATE MAILED: 11 11 93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on May 26, 1994 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), ~~one~~ (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims ~~1,2,5-7,10,13~~ 1-18 are pending in the application.
   Of the above, claims 3,4,8,9,11,12,16-18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1,2,5-7,10,13-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application should be reviewed for errors.

Claims 1, 2, 5-7, 10 and 13-15 are examined in this Office Action.

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1, 2, 5-7, 10 and 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8, 27 and 30 of copending application serial no. 07/467,888. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims embrace each other. Both sets of claims are drawn to methods of treating pathologies or diseases characterized by an accumulation of extracellular matrix using agents inhibiting TGF-beta.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 5-7, 10 and 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 12-24 of copending application serial no. 07/803,285. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims embrace each other. Both sets of claims are drawn to methods of treating pathologies or diseases characterized by an accumulation of extracellular matrix using agents inhibiting TGF-beta..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The rejection of claims 1, 2, 5-7 and 10 under 35 U.S.C. 112, first and second paragraphs, is maintained, the rejection of claim 13-15 under 35 U.S.C. 112, first and second paragraphs, is withdrawn. Applicant's arguments, filed May 26, 1992, have been considered but not found to be persuasive.

Applicants have argued that the claims 1 and 6 should not be limited merely to anti-TGF-beta antibodies because the specification on page 13, lines 25-27 and pages 24-25 specifically describe studies in which PDGF and Arg-Gly-Asp containing peptides were effective in addition to anti-TGF-beta. However, such proteins or peptides are not "TGF-beta specific inhibitory agents" as the claim now has been amended to read. Indeed, there is no indication that the peptides or protein interacts with TGF-beta. The peptide and protein are known in the art to interact with the TGF-beta binding site which is different than TGF-beta. Thus, the claims must be limited to an antibody as used by the Applicants.

Regarding claim 1 and 6, Applicants have argued that the phrase "extracellular matrix" is not vague and unclear and that more proteins than decorin and biglycan were studied. The Examiner withdraws the argument that the phrase is vague and unclear and thus the rejection under 35 U.S.C. 112, second paragraph, but maintains the rejection under 35 U.S.C. 112, first paragraph. The specification fails to present evidence showing that any other

proteins were studied and that TGF-beta stimulates their synthesis. In addition, the specification clearly states that the extracellular matrix is composed of a mixture of proteoglycans, glycoproteins and collagens assembled into a complex superstructure (page 1, lines 25-27). The arguments regarding the effect of TGF-beta on fibronectin have been considered but not found persuasive. Thus, the specification is not commensurate with the scope of the claim.

Applicants have argued that with regard to claims 1 and 6, more proteins than decorin and biglycan were studied. However, although Applicants have presented a reference showing an increase in fibronectin synthesis also occurs in addition to increases in other proteins, the term "extracellular matrix" in known in the art to encompass many proteins and Applicants have not provided evidence showing an increase in all of the components of the "extracellular matrix". Therefore, the claim must be limited to the decorin and biglycan, the components actually investigated by Applicants. Note that the stain used by Applicants is admitted by Applicants to be non-specific and does not distinguish individual components (page 4, this amendment). Since the scientific definition of "extracellular matrix" is one which includes many proteins, it is erroneous to claim an inhibition of extracellular matrix production when in fact one has achieved an inhibition of the synthesis of particular proteins. It is noted that although Applicants are permitted to be their own lexicographer, they are not permitted to misuse art recognized terms. The definition of extracellular matrix is an art recognized term encompassing more than biglycan, decorin and fibronectin. It is therefore misleading and incorrect to claim an inhibition of extracellular matrix when in fact one has obtained an inhibition of the synthesis of certain proteins known to be components of the extracellular matrix.

Applicants have argued that there has been no evidence presented to refute the statements in the specification that by inhibiting the activity of TGF-beta, the deleterious accumulation of extracellular matrix will be

suppressed. However, no such argument has been made. As stated above, the term "extracellular matrix" has an art recognized definition and Applicants are not permitted to misuse art recognized terms. Applicants have shown an increase in the synthesis of decorin and biglycan and failed to show an increase in synthesis of many of the other components comprising the "extracellular matrix". Thus the specification is not enabling for the scope of the claim.

The arguments set forth by the Examiner regarding the mechanism of action associated with the phrase "suppresses the extracellular matrix producing activity" is withdrawn. However, the withdrawal of the argument does not result in the withdrawal of the claims from being rejected under 35 U.S.C. 112, first and second paragraphs, for the other reasons as previously stated.

The rejection of claims 2 and 7 regarding limiting the the claims to the antibody actually used by Applicants is withdrawn. The claims remain rejected by virtue of dependency.

The rejection of claim 5 regarding the limitation to glomerulonephritis is maintained. Applicants have argued that the Examiner has failed to present evidence showing that the claimed methods would work in treating other diseases such as cirrhosis and ARDS. However, Applicants merely state on page 1 of the specification that ARDS and cirrhosis are diseases characterized by accumulation of extracellular matrix and fail to present evidence showing that the extracellular matrix accumulation is related to TGF-beta. If the accumulation of extracellular matrix is not related to TGF-beta, then methods of inhibiting TGF-beta activity would not have an effect on those diseases. Applicants have failed to present evidence supporting their assertions and the implicit assertion that all deleterious extracellular matrix accumulations are related to TGF-beta is speculative, lacking evidence to the contrary.

The rejection of claims 6 and 13 regarding the failure of the antibodies to inhibit accumulation is withdrawn.

The rejection of claims 10 and 13 regarding the limitation of the claim to kidney tissue or kidney cells is withdrawn.

The clarification of Figure 1 is noted.

The rejection of claims 1, 2, 5-7, 10 and 13-15 under 35 U.S.C. 112, first paragraph is withdrawn.

Claims 1, 2, 5-7, 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding independent claims 1 and 6, the claims have been amended to contain the phrase "a TGF-beta specific inhibitory agent" (claim 1) or "a TGF-beta specific agent". The phrases are vague and unclear since the type of agent is not apparent. Applicants presumably are intending to claim the antibody to TGF-beta since the peptides and PDGF used as blocking agents do not interact with TGF-beta per se but block the binding site of TGF-beta to the TGF-beta receptor. Thus, the peptides and PDGF cannot be considered to be specific to TGF-beta.

Claims 1, 6 and 10 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to an antibody. See MPEP 706.03(n) and 706.03(z). Applicants have injected an antibody to TGF-beta into an animal model (rat) of glomerular nephritis and have shown a decrease in the amount of extracellular matrix occurring in the antibody treated animals. Applicants have failed to present evidence showing that administration of peptides or PDGF would have the same effect. It is not apparent that peptides or PDGF would have the same effect as the antibodies since the other agents are not specific for TGF-beta nor is it apparent how such factors could localize to the desired site to exert any influence in an in

vivo setting since hydrolysis of injected proteins is well known and rats endogenously produce PDGF. In addition, Applicants have failed to disclose evidence showing that the peptides would work in an in vivo setting since the experimental system used depended upon artifically activated TGF-beta and it is not apparent that such levels of activated TGF-beta would be produced by tissues in an in vivo setting. Thus, claims 1 and 6 must be limited to the antibody.

The rejection of claims 1, 6, and 10 under 35 U.S.C 102(b) is withdrawn; the rejection of claims 13-15 under 35 U.S.C. 102(b) is maintained. Applicants have argued that Bassol fails to treat pathologies; however, claims 13-15 do not claim treating pathologies and do not claim a specific inhibitor. Thus, the reference anticipates the claims.

Since the rejection of claims 1, 6 and 10 under 35 U.S.C. 102(b) has been withdrawn, Applicant's arguments are moot.

The rejection of claims 1, 2 5-7, 10 and 13-15 under 35 U.S.C. 103 as being unpatentable over Flanders taken with Harper is withdrawn in view of a new ground of rejection. Therefore, Applicant's arguments are moot.

Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 103 as being unpatentable over Connor et al. Connor discloses treating an in vitro model system of intraocular fibrosis, a pathology characterized by extracellular matrix accumulation (page 1661, column 2, first full paragraph) which is known to produce TGF-beta (Abstract) by using antibodies to TGF-beta (Abstract). Connor further discloses that 84-100% of the TGF-beta activity could be blocked using specific antibodies to TGF-beta (Abstract). Connnor differs from the claims in that the reference fails to disclose in vivo usage of the antibodies for treating the pathology. However, Connor clearly suggests such a treatment on page 1665, second column, last paragraph, wherein it is stated "The final determination of the role of TGF-beta in this disease process awaits the ability to block its activity and assess if this can retard or arrest

fibrosis". Thus, it would have been obvious to one of ordinary skill to administer the antibodies in vivo in order to determine the therapeutic effect of the antibodies on disease progression. One of ordinary skill would have had a reasonable expectation of success in achieving retardation of the ocular disease by using the antibody to TGF-beta since the use of antibodies to target specific cells in vivo is a technique old and well known in the art and Connor clearly shows the ability of the antibody to block the TGF-beta effect in vitro. Thus, the question as to whether the antibody could reach the target site in order to inhibit the TGF-beta is rendered moot in view of the known and widely accepted use of antibodies to bind to a variety of cell types in a variety of locations.

Regarding claims 2 and 7, Connor discloses use of antibodies to TGF-beta (Abstract).

Accordingly, the modification of the in vitro method of Connor by using the antibody in an in vivo treatment method as further suggested by Connor in order to obtain a method for treatment of pathologies characterized by a deleterious accumulation of extracellular matrix was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 5 and 10 are rejected under 35 U.S.C. 103 as being unpatentable over Connor et al as applied to claims 1, 2, 6 and 7 above, and further in view of MacKay et al. Claims 1, 2, 6 and 7 were rejected under 35 U.S.C. 103 for reasons as stated above. MacKay discloses the relationship between TGF-beta and the proliferation of glomerular cells and the accumulation of mesangial matrix in progressive glomerular nephritis. It would have been obvious to one of ordinary skill to substitute glomerular

tissue for the ocular tissue of Connor in order to obtain a method of treating pathologies characterized by an accumulation of extracellular matrix once the ability of the antibody to block TGF-beta activity was successfully demonstrated. It would have been obvious to apply the concept to diseases characterized by excess TGF-beta production and having increased extracellular matrix production since the ability of the antibody to bind to TGF-beta is irrespective of tissue location or cell type, lacking evidence to the contrary.

Regarding claims 5 and 10, glomerular nephritis is a progressive disease of glomerular cells, which are a part of the kidney tissue.

MacKay provides the motivation to combine the references on page 1160, Abstract, wherein it is stated "The presence of TGF-beta receptors on intact glomeruli and on each glomerular cell type and the demonstrated responsiveness of these cells to TGF-beta combine to suggest that potentially important interactions may occur between resident glomerular cells and TGF-beta in vivo". Thus, it would have been obvious to one of ordinary skill to use an antibody to TGF-beta in order to interfere with the interaction between TGF-beta and glomerular cells in an in vivo setting since antibodies are known to be able to localize to particular tissues in vivo.

Accordingly, the modification of the method of Connor by using the antibody to treat tissues suffering from glomerular nephritis as suggested by Mackay in order to obtain a method for treatment of pathologies characterized by an accumulation of extracellular matrix was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217.

SUZANNE E. ZISKA
PATENT EXAMINER
GROUP 1800

1/5/93